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Autosomal Dominant Transmission of Familial Laterality Defects

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Heterotaxy results from failure to establish normal left-right asymmetry during embryonic development. Most familial cases are thought to be autosomal recessive. We have identified a family in which 4 individuals from 3 generations manifest laterality defects. Twenty-five family members have been examined. Two have complete reversal of normal laterality (situs inversus) while 2 others have asplenia, midline liver, and complex cardiac malformations (situs ambiguus). Two additional obligate gene carriers are anatomically normal (situs solitus). Male-to-male transmission confirms autosomal inheritance. Identification of this family establishes an autosomal dominant form of laterality defect, suggesting that a portion of sporadic cases may be new-mutation dominant or unrecognized familial cases. The finding of all forms of laterality (solitus, ambiguus, and inversus) among obligate disease gene carriers within a single family may be relevant to genetic evaluation and counseling in apparently isolated patients with laterality disturbance.

KEY WORDS: heterotaxy, situs inversus, situs ambiguus, asplenia, polysplenia, dextrocardia, autosomal dominant inheritance

INTRODUCTION

Many unpaired organs become asymmetrically distributed with respect to the midline during human development. The direction of asymmetry is invariant rather than random within and among individuals. Termed situs solitus, this stereotypic organ placement is characterized by consistent left-sided placement of spleen, stomach, and cardiac apex.

Two classes of abnormal left-right axis development have been described. Complete asymptomatic reversal of normal organ position (situs inversus) is the first of these and occurs in 1 in 8,000 to 1 in 11,000 individuals [Afzelius and Mossberg, 1994]. Usually no other abnormalities are identified, but as many as 25% of affected individuals manifest situs inversus as part of the immotile cilia syndrome (ICS). Individuals with ICS suffer the sequelae of ciliary dysfunction, which include sinusitis, chronic bronchitis and bronchiectasis, and (in males) infertility. Only approximately half of all ICS patients are situs inversus (a combination referred to as Kartagener syndrome), while the remainder are situs solitus [Moreno and Murphy, 1981; Sturgess et al., 1986].

Heterotaxy, the second class, is characterized by randomization rather than reversal of normal left-right asymmetry [McKusick, 1995]. In affected individuals this randomization results in situs ambiguus, typically presenting with complex cyanotic heart defects, altered lung lobation, splenic abnormalities (asplenia, polysplenia, or right-sided spleen), and malposition of the gastrointestinal tract. Although it is often fatal within the first few years of life, the natural history of heterotaxy in individual patients depends largely on the severity of the heart malformation. Ciliary structure and function are normal in these individuals.

Familial transmission of laterality defects has been thought to be largely (for heterotaxy) or almost entirely (for ICS) due to autosomal recessive inheritance. Furthermore, the nature of the laterality defect appears to breed true: situs ambiguus in a family with ICS is extremely rare [Rott, 1979; Teichberg et al., 1982; Schidlow et al., 1982], as is situs inversus among relatives of individuals with heterotaxy [Burn, 1991]. Here we present an unusual family with heterotaxy in which laterality defects ranging from asymptomatic situs inversus to fatal situs ambiguus are transmitted by autosomal

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dominant inheritance with reduced penetrance. The observation of such a family may alter prevailing opinion regarding the genetics of sporadic and familial cases and has clinical implications for their routine evaluation and genetic counseling.

CLINICAL REPORT

Overview of Family

The pedigree (Fig. 1) indicates that 24 individuals have received physical examinations. Eighteen individuals, including all of the obligate gene carriers, underwent complete 2-dimensional pulsed and color Doppler echocardiogram. Spleen, stomach, and liver position were also determined to be solitus or inversus, the cardiac position as either levo- or dextrocardia, and the aortic arch as either right- or left-sided. In addition, systemic and pulmonary venous connections were evaluated. Ciliary biopsies and routine G-band lymphocyte karyotypes were performed on a small number of selected family members.

At least 4 individuals in 3 generations manifest laterality defects: 2 with asymptomatic, complete situs inversus (II-3 and II-8) and 2 with situs ambiguus (III-9 and IV-1). Male-to-male transmission is seen from II-8 (situs inversus) to III-20 (situs solitus) to IV-1 (situs ambiguus). Two obligate gene carriers, II-2 and III-20, are asymptomatic and show no anatomic abnormalities by physical examination and imaging studies. None of the individuals examined reports recurrent respiratory tract infections, hearing difficulties, decreased ability to smell, or infertility. Electron microscopic examination of ciliary biopsies from II-8, III-20, and IV-1 showed no structural abnormality. Individuals II-2, II-3, II-8, and IV-1 had normal karyotypes.

Patient III-9

Post-mortem examination of this fetus showed growth parameters appropriate for his gestational age of 21 weeks. No external anomalies were noted. Internal examination showed bilateral tri-lobed lungs, common atrioventricular canal defect, atria of right-sided morphology bilaterally, pulmonary artery atresia, centrally placed liver, and asplenia. The central nervous system was not examined. Chromosome analysis showed 46,XY karyotype.

This patient's mother has had 6 miscarriages. Four were first-trimester missed abortions and 2 were due to common chromosomal aneuploidies. Post-mortem examination was not performed in any of these cases.

Patient IV-1

This term infant became cyanotic during the first day of life. Chest X-ray (Fig. 2) showed dextrocardia, and further imaging studies showed transposition of the great vessels, bilateral superior venae cavae, pulmonary artery atresia, common atrioventricular canal, midline liver, and asplenia. No external anomalies were identified. A modified right Blalock-Taussig shunt was performed on the 6th day of life. At age 2½ years the Blalock-Taussig shunt was closed and a hemi-Fontan procedure was performed. Ciliary biopsies of the tra-

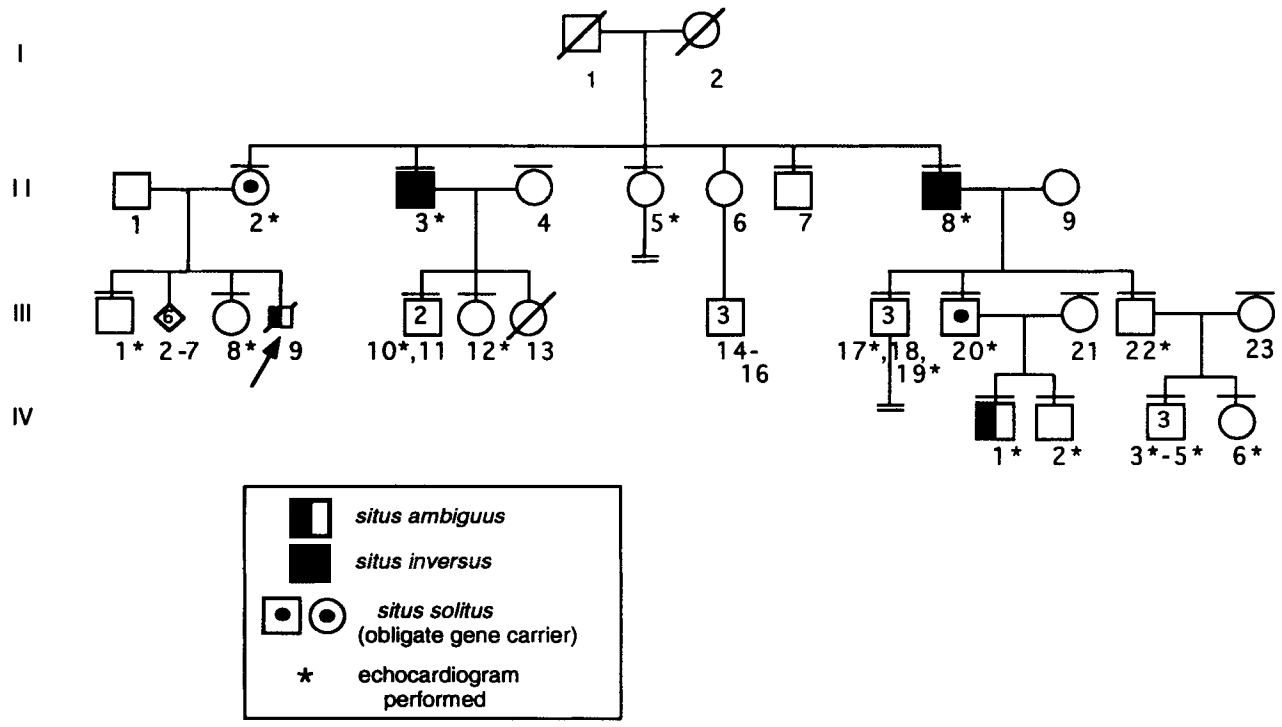

Fig. 1. Pedigree of family with autosomal dominant laterality defects. ◧, situs ambiguus; ■, situs inversus; ⊡ ⊙, situs solitus (obligate gene carrier); *, echocardiogram performed.

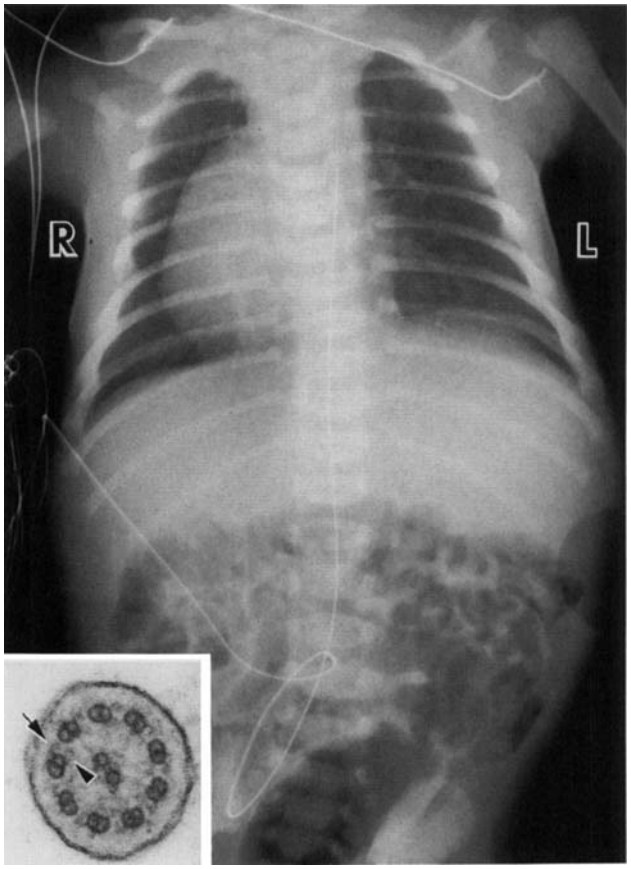

Fig. 2. Newborn X-ray of patient IV-1 showing dextrocardia. Inset shows transmission electron micrograph of cilia biopsy from the same individual; arrows indicate normal dynein arms forming bridges between sets of microtubules.

chea taken preoperatively showed no structural abnormality (Fig. 2).

DISCUSSION

We describe a family in which laterality defects segregate as an autosomal dominant trait with reduced penetrance. Four affected individuals have been identified: 2 with complete reversal of normal left-right asymmetry (situs inversus) and 2 with situs ambiguus manifesting as complex heart malformations, midline liver, and asplenia. Two obligate disease gene carriers show no situs abnormalities by physical examination and ultrasonography. Furthermore, 15 additional relatives have been studied by ultrasound, and none displays abnormal laterality. Although the presence of situs inversus suggests the possibility of ICS, the absence of upper respiratory disease in this family, the presence of fertile affected and obligate-carrier males, and normal ciliary biopsies from 2 affected individuals and one obligate gene carrier preclude this diagnosis.

Affected individuals in multiple generations and male-to-male transmission support an interpretation of autosomal dominant inheritance of a mutant gene affecting left-right asymmetry in this family. Pedigree inspection shows no evidence for parent-of-origin effects on phenotype: One of the individuals with situs ambiguus is the offspring of a female obligate carrier, and the other descends from a male obligate carrier. The absence of affected females could be due to chance or to sex-limited expression. No convincing evidence of anticipation is identified.

This family shows a striking phenotypic similarity to *situs inversus viscerum* (*iv*), a spontaneous murine mutation characterized by situs patterns ranging from solitus to ambiguus to inversus among *iv/iv* homozygotes [Layton, 1976]. Segregating as autosomal recessive mutations, *iv* and the allelic *legless* have been mapped to distal mouse chromosome 12 [Brueckner et al., 1989; Hanzlik et al., 1990; Singh et al., 1991; McGrath et al., 1992]. It is possible that the family we describe here, although showing a dominant inheritance pattern, harbors a mutation in the human homolog of *iv*. The difference in inheritance pattern could be attributed to allelic heterogeneity, e.g., a null in the murine *iv* and a dominant-negative or gain-of-function mutation in this family. Alternatively, the same mutation could lead to different phenotypic inheritance patterns due to variations in modifier genes or, as demonstrated by Layton et al. [1993], to the presence of low-penetrance mutant alleles of other genes directly involved in determining laterality. *Inversion of embryonic turning* (*inv*), another autosomal recessive murine model of laterality defects, shows less similarity to human autosomal dominant heterotaxy. Most *inv/inv* homozygotes display situs inversus while the remainder are situs ambiguus; situs solitus has not been detected [Yokoyama et al., 1993]. *Inv* has been mapped to mouse chromosome 4. To date neither *inv* nor *iv* has been isolated and characterized.

Niikawa et al. [1983] described 2 brothers with situs ambiguus whose father had situs inversus. Although smaller, this family appears quite similar to the one we report here in both inheritance pattern and in the finding of situs ambiguus and situs inversus among affected individuals. Most reported familial cases appear to show autosomal recessive inheritance with multiple affected sibs in a single generation, often born to consanguineous parents [Brueckner et al., 1991]. Apparent X-linked transmission has been proposed in 2 families [Mathias et al., 1987; Mikkila et al., 1994], and one of these has been utilized to establish linkage of a gene for heterotaxy to Xq24-q27.1 [Casey et al., 1993]. The identification of the family reported here raises the possibility that some isolated and familial heterotaxy cases may represent dominant inheritance, either through new mutation or passage of the disease gene from a nonmanifesting parent.

The documentation of situs ambiguus and situs inversus inherited as an autosomal dominant trait with reduced penetrance may have practical implications for the clinical evaluation and genetic counseling of isolated cases of laterality defects. Individuals with asymptomatic situs inversus may be at risk of having offspring with situs ambiguus and its accompanying morbidity and mortality. First- and second-degree relatives of individuals with situs ambiguus should be ex-

amined carefully for subclinical manifestations of laterality defects, including situs inversus or mild manifestations of situs ambiguus (e.g., minor cardiac or venous anomalies, asplenia, right-sided stomach, intestinal malrotation). Given the many reports of chromosomal anomalies associated with laterality defects, it may be appropriate to perform routine karyotyping [Koiffmann et al., 1993].

In conclusion, laterality defects have previously been thought to be due to autosomal recessive inheritance, with situs ambiguus characterizing the phenotype. We now report a family with autosomal dominant transmission and reduced penetrance in which all classes of visceral situs are seen among obligate disease gene carriers. We suggest that current clinical evaluation and genetic counseling in both sporadic and familial cases of laterality disturbance might be modified by the information derived from the identification of this family.

NOTE ADDED IN PROOF

Alonso et al. [1995] have recently described several families with apparent autosomal dominant inheritance of laterality defects, providing further support for the suggestion that this mode of transmission may be much more common than previously recognized.

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